



SUICIDE AND BRAIN CHEMICAL CHANGES WITH ALTITUDE

Converging Evidence and Research Directions

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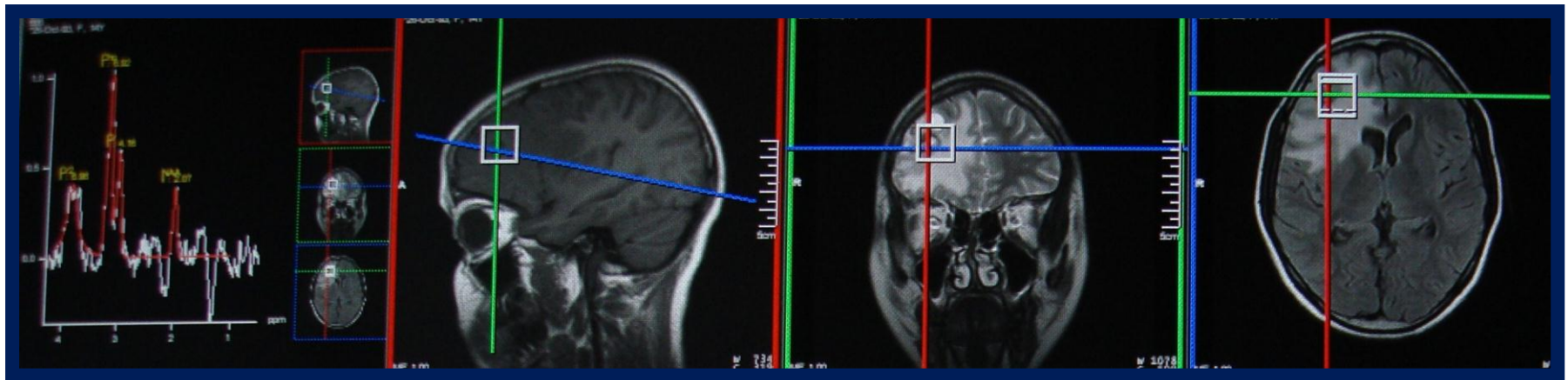
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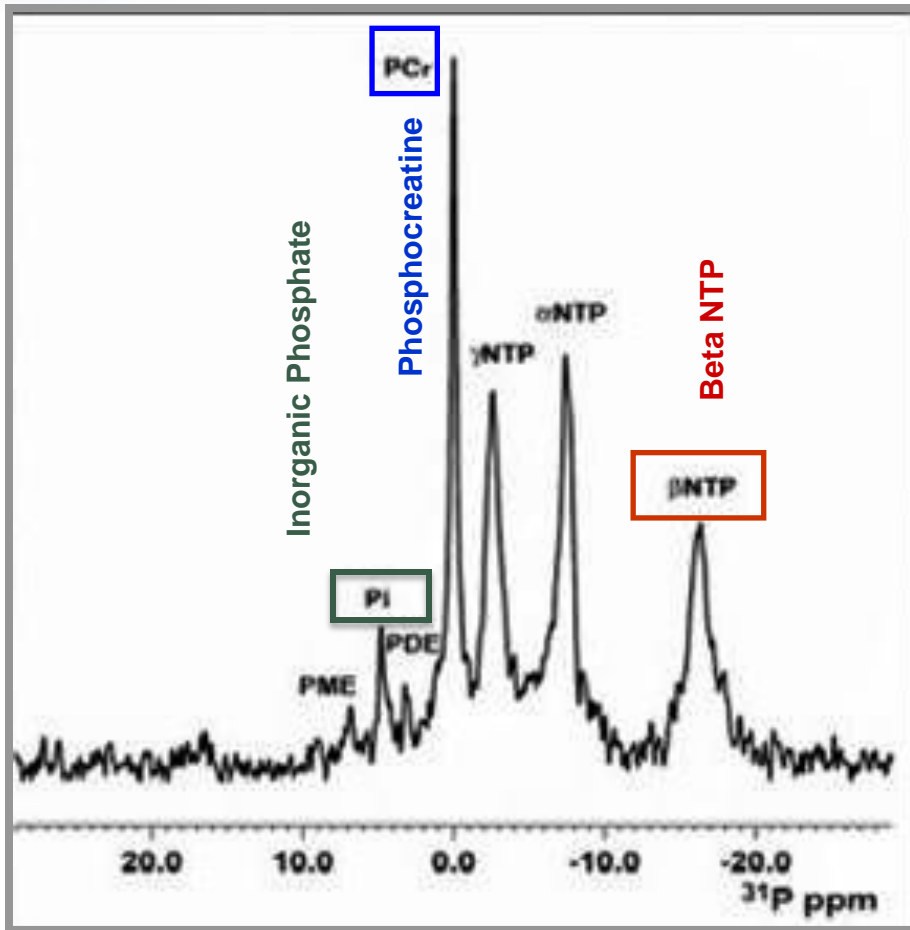
Outline / Objectives

- **Describe neuroimaging methods for measuring energy metabolism in the brain**
- **Define “hypobaric hypoxia”**
- **Review the data regarding the effects of altitude on:**
 - Active duty military personnel
 - Civilian rates of depression and suicide
- **Present a potential nutritional supplement strategy for improving brain energy metabolism, and neuroimaging research results to date**

MEASURING ENERGY METABOLISM IN THE BRAIN



Phosphorus Magnetic Resonance Spectroscopy (^{31}P -MRS)



PME

Phosphomonoester

Pi

Inorganic Phosphate

PDE

Phosphodiester

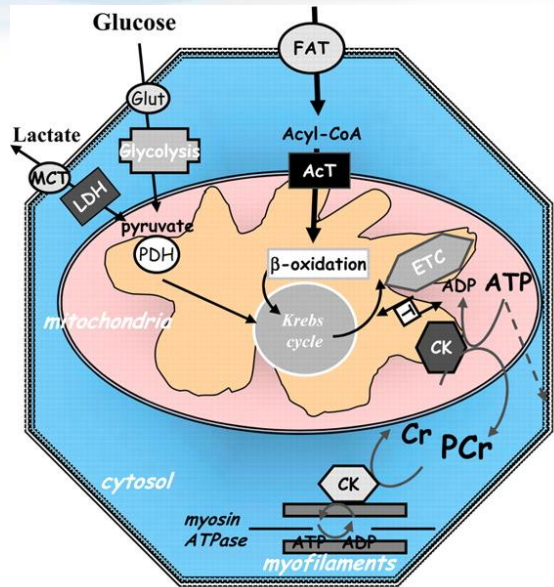
PCr

Phosphocreatine

β -ATP

Beta Nucleoside Triphosphate

The Creatine Kinase (CK) Reaction



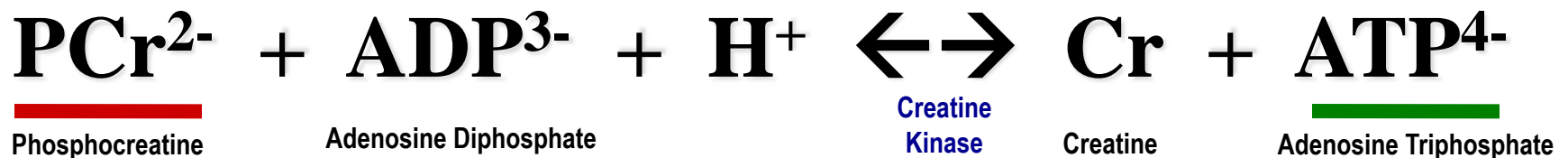
Ventura-Clapier et al. *Cardiovascular Research* 2008;79(2):208-217

5 Nutrients that Enhance ATP and Improve Cognition

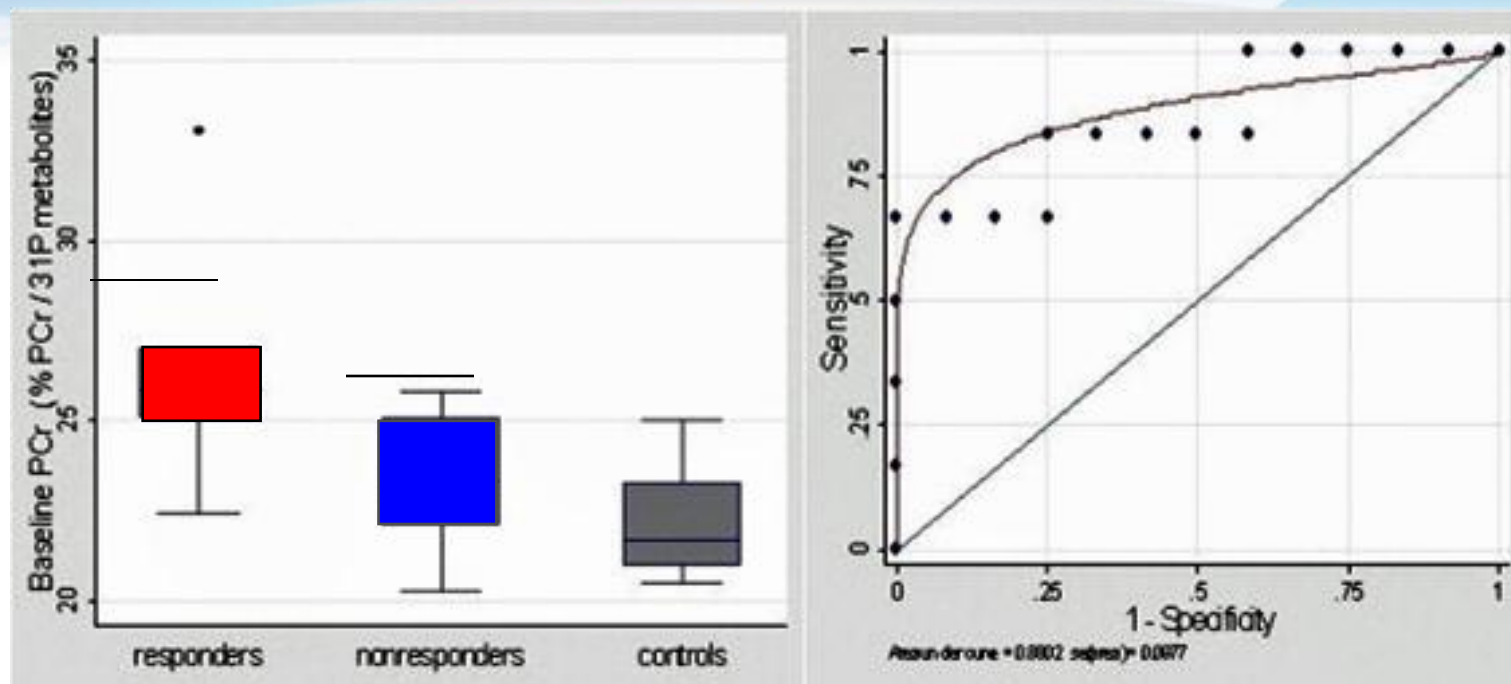
- Glucose
- **Oxygen** ←
- Pyruvate
- **Creatine** ←
- L-Carnitine

Owen et al. *Nutrients* 2011;3(8):735-55

CK



Is Phosphocreatine (PCr) a BIOMARKER for MDD Treatment Response?



Baseline PCr Levels in:

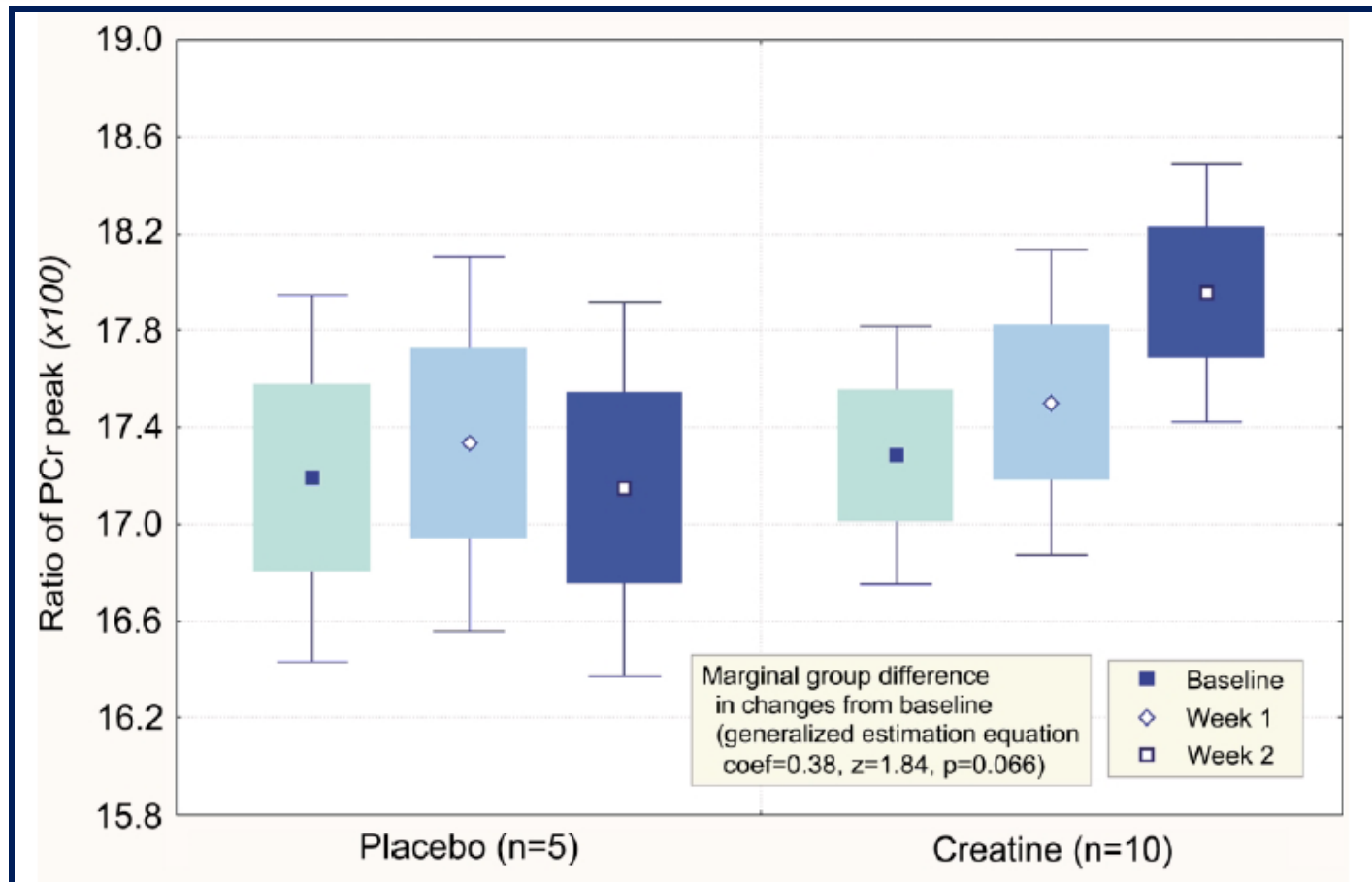
-  MDD Treatment Responders
-  MDD Non-Responders
-  Controls

“Baseline PCr” Predicts Treatment Response:

- Sensitivity = 83%
- Specificity = 75%
- Area Under the ROC Curve = 0.88

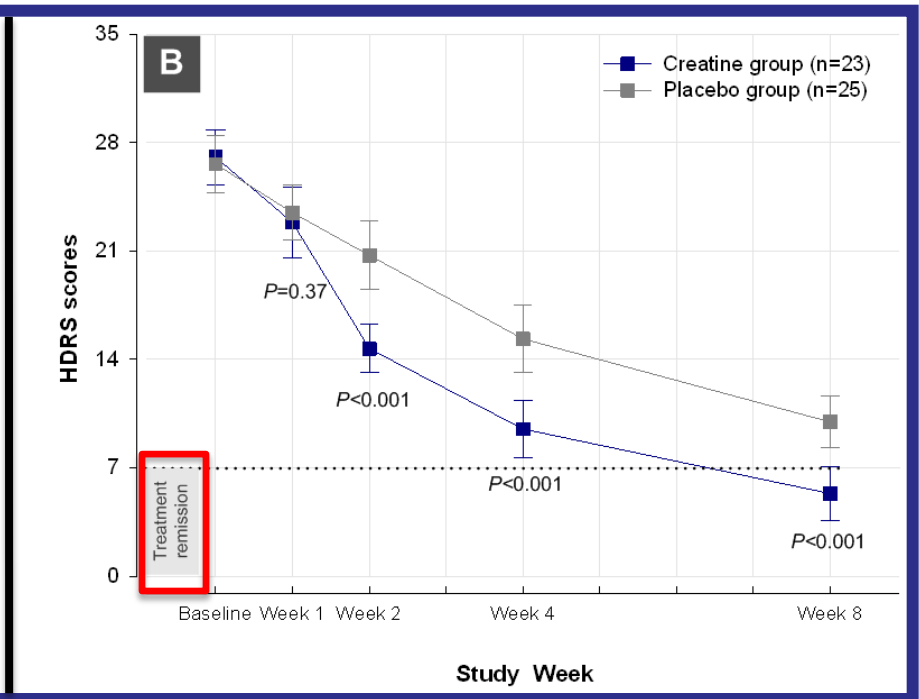
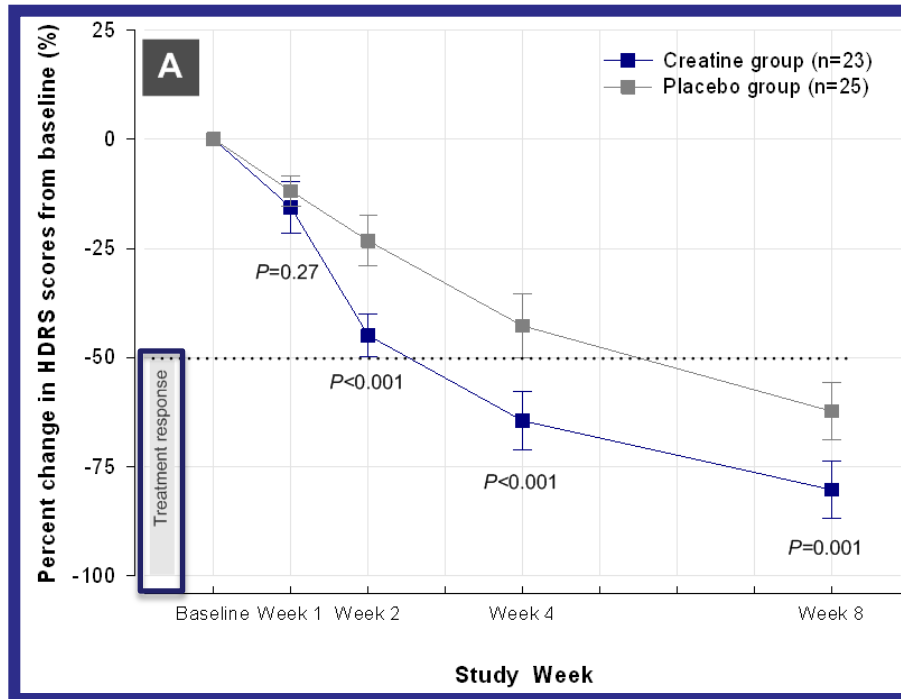
Iosifescu et al. *Biological Psychiatry* 2008; 63(12):1127-34

Brain Phosphocreatine (PCr) Levels Are Increased by the Nutritional Supplement Creatine



Lyoo et al. Multinuclear magnetic resonance spectroscopy of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate. *Psychiatry Res* 2003;123(2):87-100

SSRI Augmentation in Adult Major Depression: RCT of *Creatine* vs. *Placebo* added to Lexapro®



[A] CLINICAL RESPONSE: Percent decrease in Hamilton Depression Rating Scale scores (RESPONSE = ↓50%)

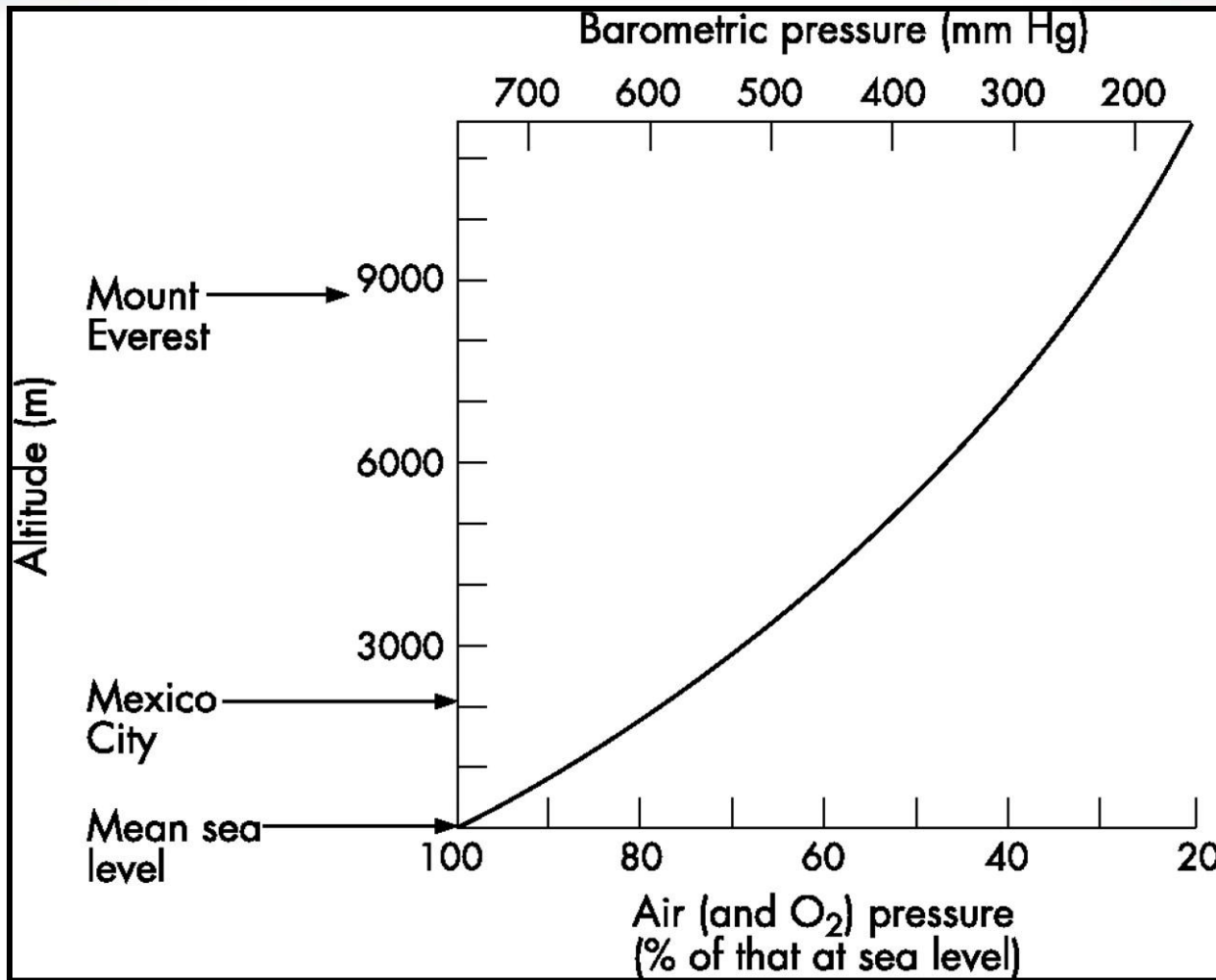
[B] CLINICAL REMISSION: Change in HDRS scores from baseline to 8 weeks (REMISSION ≤ 7)

Lyoo, Yoon, Kim and Renshaw, accepted by *American Journal of Psychiatry*

HYPOBARIC HYPOXIA



Altitude, Barometric Pressure, Air Pressure and Oxygen Tension



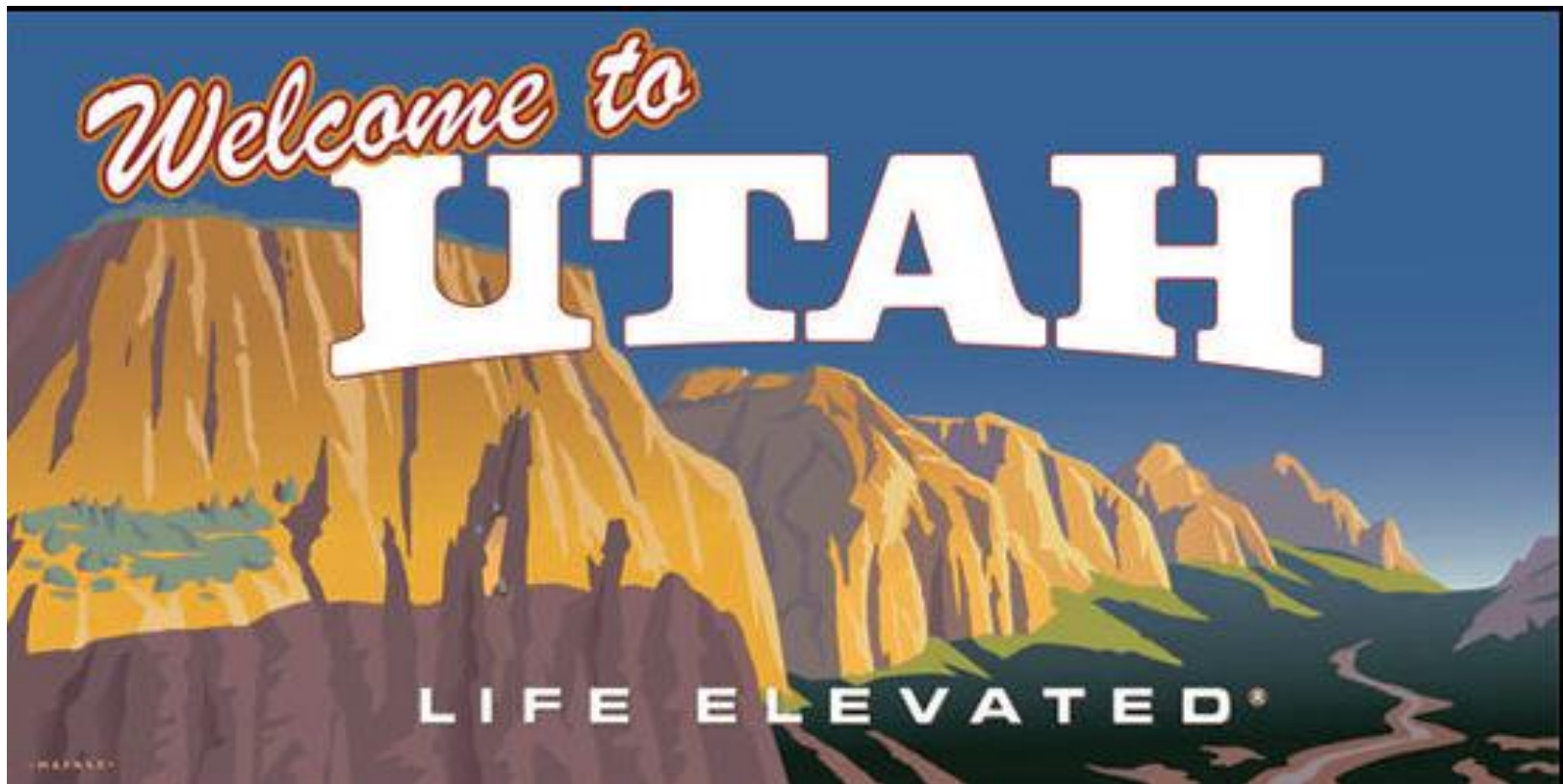
Clarke C. *Postgraduate Medical Journal* 2006; 82(973):748-753

Altitude Conversion for Barometric Pressure, Partial Pressure of Oxygen, and the Equivalent Oxygen Concentration at Sea Level

Altitude (Meters)	Altitude (Feet)	Barometric Pressure (P_B)	Partial Pressure of Oxygen (PiO_2)	Equivalent O_2 Concentration at Sea Level (FiO_2)	Decrease In FiO_2
Sea Level	Sea Level	759.6	149.1	0.209	0%
1,000	3,281	678.7	132.2	0.185	12%
1,219	4,000	661.8	128.7	0.180	14%
1,500	4,921	640.8	124.3	0.174	16%
1,524	5,000	639.0	123.9	0.174	17%
1,829	6,000	616.7	119.2	0.167	20%
2,000	6,562	604.5	116.7	0.164	22%
2,134	7,000	595.1	114.7	0.161	23%
2,438	8,000	574.1	110.3	0.155	26%
8,839	29,000	253.0	43.1	0.060	71%

Auerbach PS, Wilderness Medicine 5th Edition (2007)

What are the Effects of Altitude?

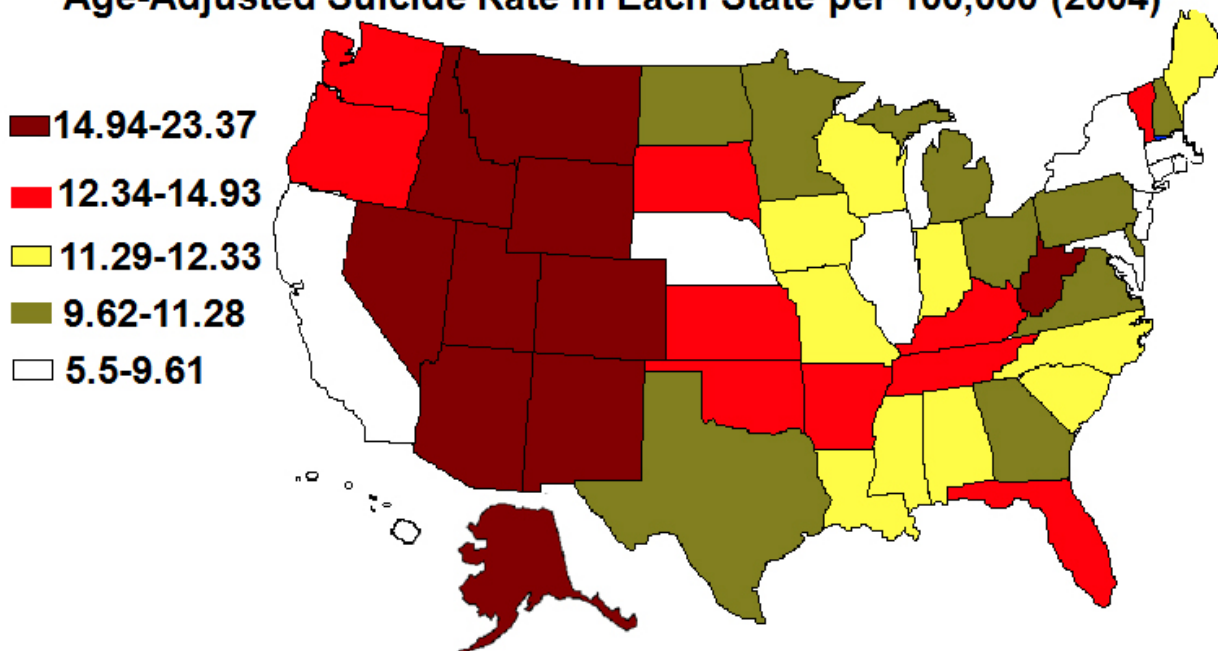


The Salt Lake Tribune

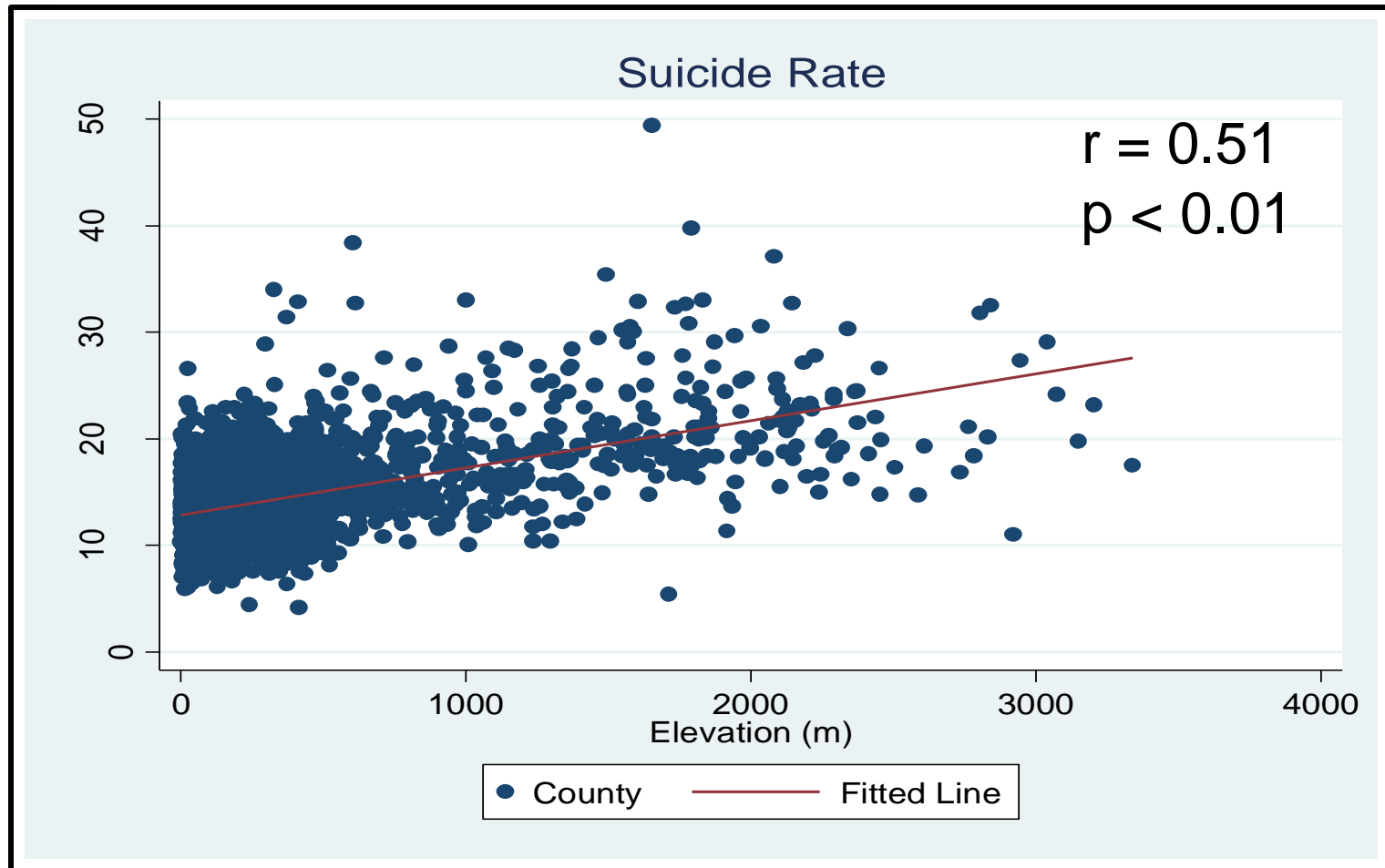
February 19, 2012

Utah has one of the highest suicide rates in nation

Age-Adjusted Suicide Rate in Each State per 100,000 (2004)



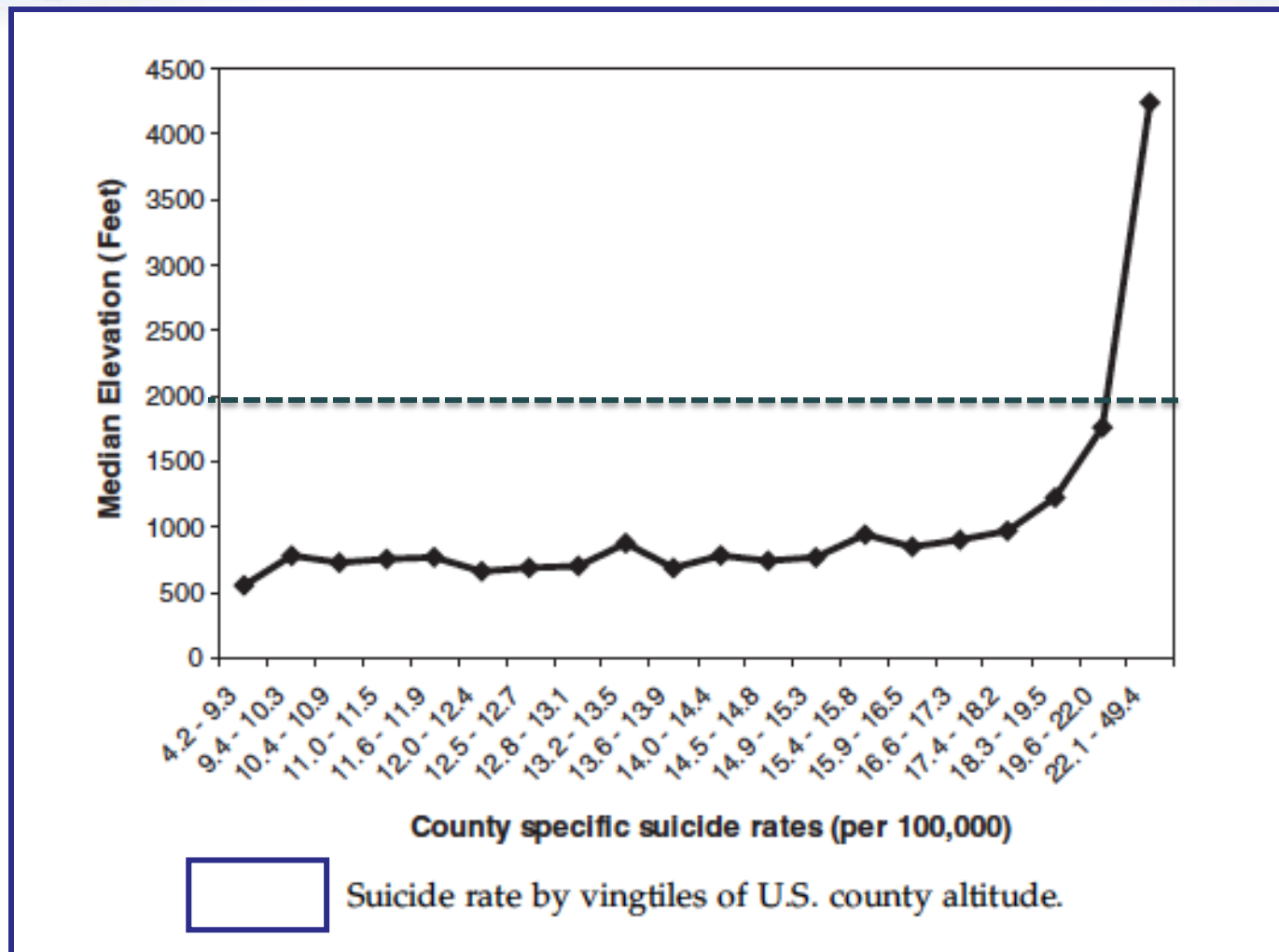
Age-Adjusted Suicide Rate (1979-1998) vs. the Mean Altitude of U.S. Counties



Kim et al. *American Journal of Psychiatry* 2011;168(1):49-54

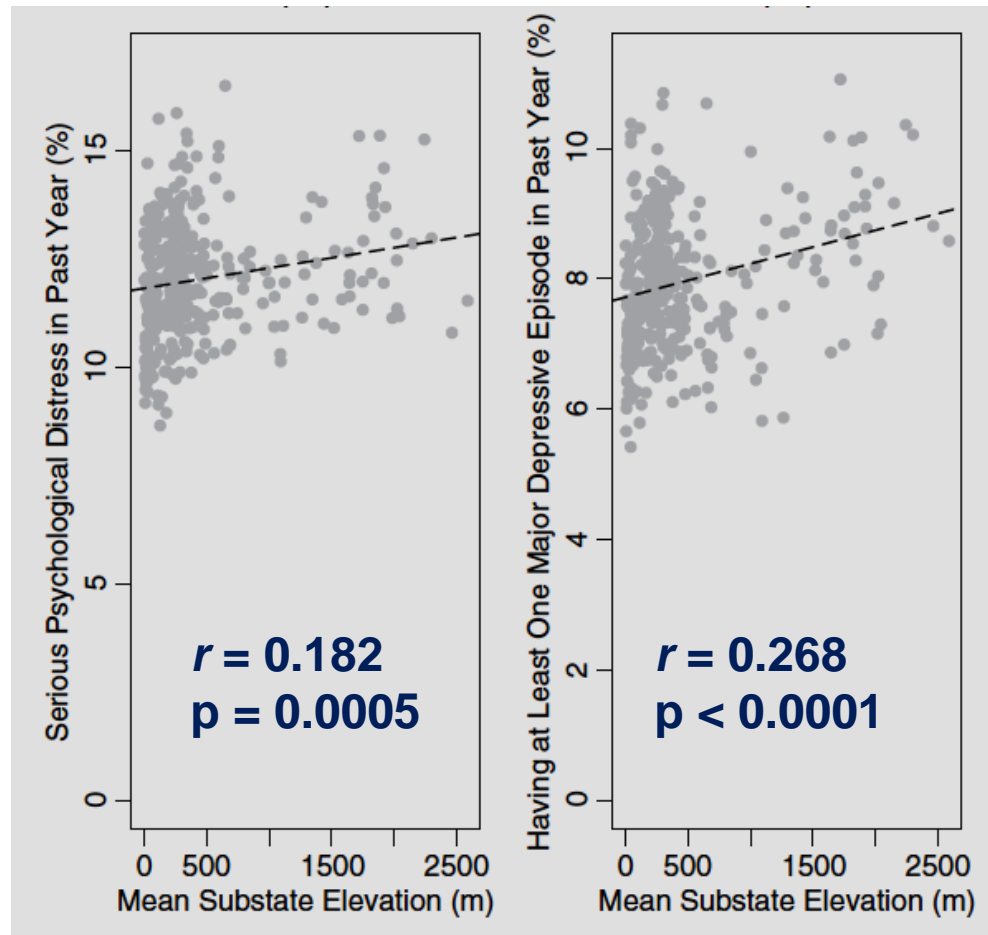
U.S. Suicide Rate by Altitude

Brenner et al. Positive association between altitude and suicide in 2584 U.S. counties.
High Altitude Medicine & Biology 2011; 12(1):31-5



N.B. there is a negative correlation ($r = -0.31$; $p < 0.001$) between county altitude and all-cause mortality.

Altitude and Psychological Distress (LEFT) and 12-Month Incidence of Major Depressive Episode (RIGHT)



DelMastro et al. *Journal of Affective Disorders* 2011; 129(1-3):376-9

Hematological and Physiological Adaptations Following 46 Weeks of Moderate Altitude Residence

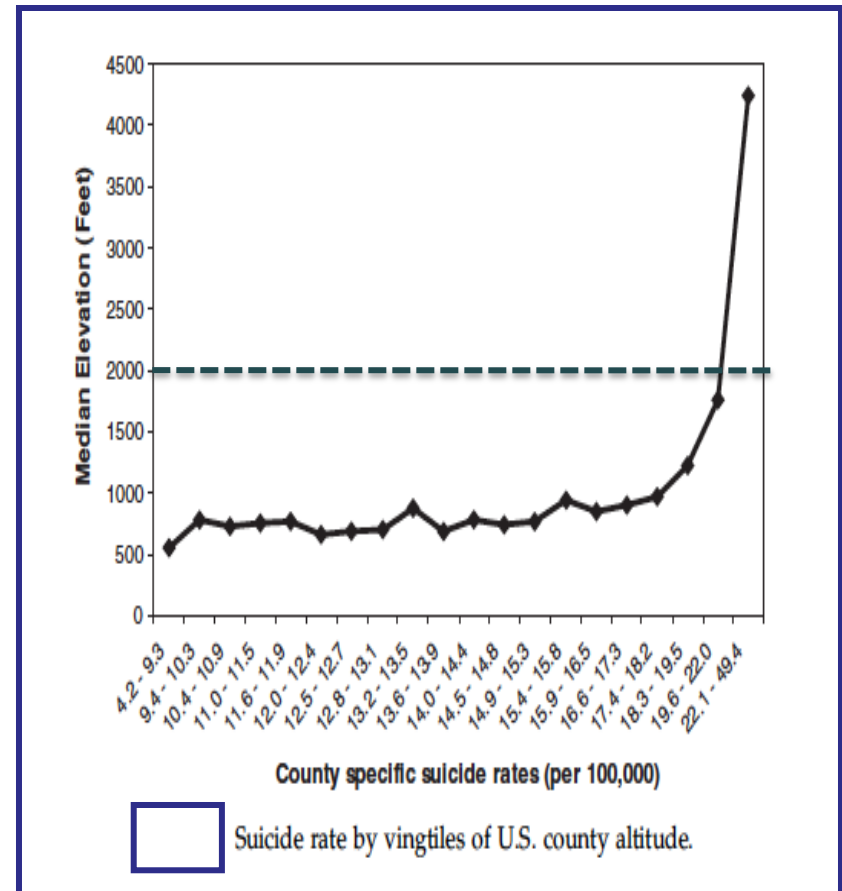
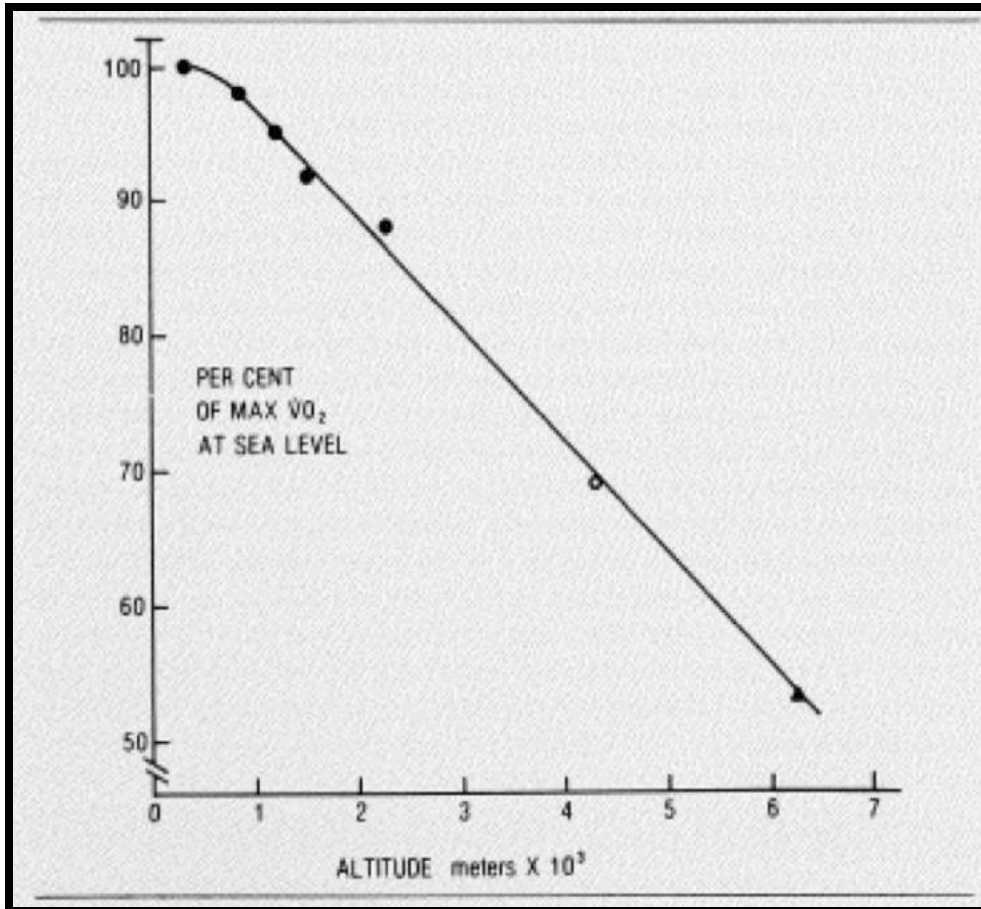
(Brothers et al. *High Alt Med Biol* 2010;11(3):199-208)

- Study conducted at the U.S. Air Force Academy (Altitude = 2210 meters; 7250 feet)
- Fourth Class (freshmen) divided into 2 groups: Those from Sea Level vs. Moderate Altitude (≥ 1500 meters)
- After **46 Weeks**, the Moderate Altitude group continued to show:
 - Higher hemoglobin & hematocrit levels
 - Higher ferritin levels (59%)
 - Faster 1.5 mile times (5.4%)
 - Better running economy (6.6%)
 - Higher physical fitness scores (13.9%)
 - Higher VO_2 max (5.9%)



Starting at an Altitude of 700 Meters, VO₂ Max Declines by 8% Every 1000 m

Grover et al. Cardiovascular adaptation to exercise at high altitude.
Exercise and Sport Sciences Reviews 1986; 14(1):269-302



Mood Disturbances Endure After 90 Days of High-Altitude Military Training

(Naval Health Research Center, Report 03-32; Bardwell et. al 2003)

- Marines training at altitude for 90 days at the Mountain Warfare Center (1970 meters; 6400 feet)
- Profile of Mood States (POMS) collected at Baseline, at Completion of Training, then 30 and 90 days Post-Training

	Norms ^f			Marines			
	College Males	Adult Males (age 18-65)	Male Psychiatric Outpatients ^h	Baseline	Post	30 Post	90 Post
Tension	10.70 ^{g**}	12.30 ^{g**}	18.4	7.42 (.57) ^{a**; b**; c*}	9.55 (.73) ^{a**}	9.80 (.93) ^{b**}	9.77 (.94) ^{c*}
Depression	8.60	8.30	22.3	7.24 (1.08) ^{a**; b*; c**}	10.41 (1.30) ^{a**}	10.67 (1.63) ^{b*}	11.61 (1.57) ^{c**}
Anger	8.90	9.20	13.5	9.11 (.96) ^{a**; b**}	13.31 (1.20) ^{a**; i}	12.51 (1.57) ^{b**; i}	11.68 (1.47) ⁱ
Vigor	16.90 ^{g**}	16.30 ^{g**}	11.3	13.08 (.77)	14.29 (.85) ⁱ	12.82 (1.07) ⁱ	14.73 (.80)
Fatigue	9.00 ^{g**}	7.00	10.1	6.07 (.64) ^{a**; b**; c*}	9.95 (.74) ^{a**; d*; i}	10.53 (1.06) ^{b**; e*; i}	7.91 (.84) ^{c*; d*; e*}
Confusion	7.10 ^{g*}	6.70	12.4	5.91 (.48) ^{a*; b**; c*}	6.79 (.58) ^{a*}	7.64 (.73) ^{b**}	7.09 (.69) ^{c*}
Total	27.50	27.20	65.4	22.66 (3.42) ^{a**; b**; c*}	35.72 (4.10) ^{a**}	38.33 (5.59) ^{b**}	33.34 (5.23) ^{c*}

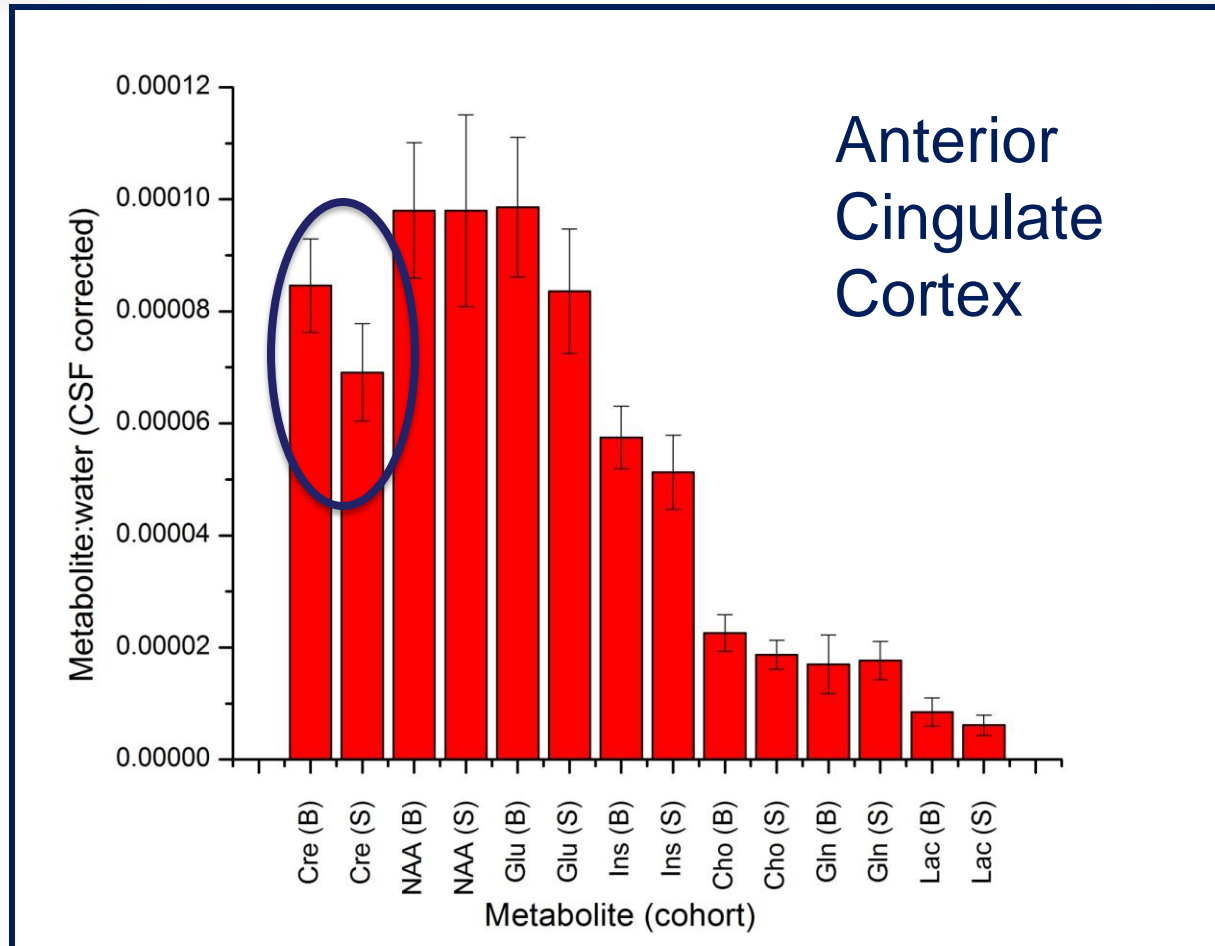
CONCLUSION: *“Rigorous military training in challenging environments may result in enduring mood symptoms that approach levels of clinical significance. Such dysphoria may have implications for readiness for duty and performance of critical tasks.”*

Current Studies

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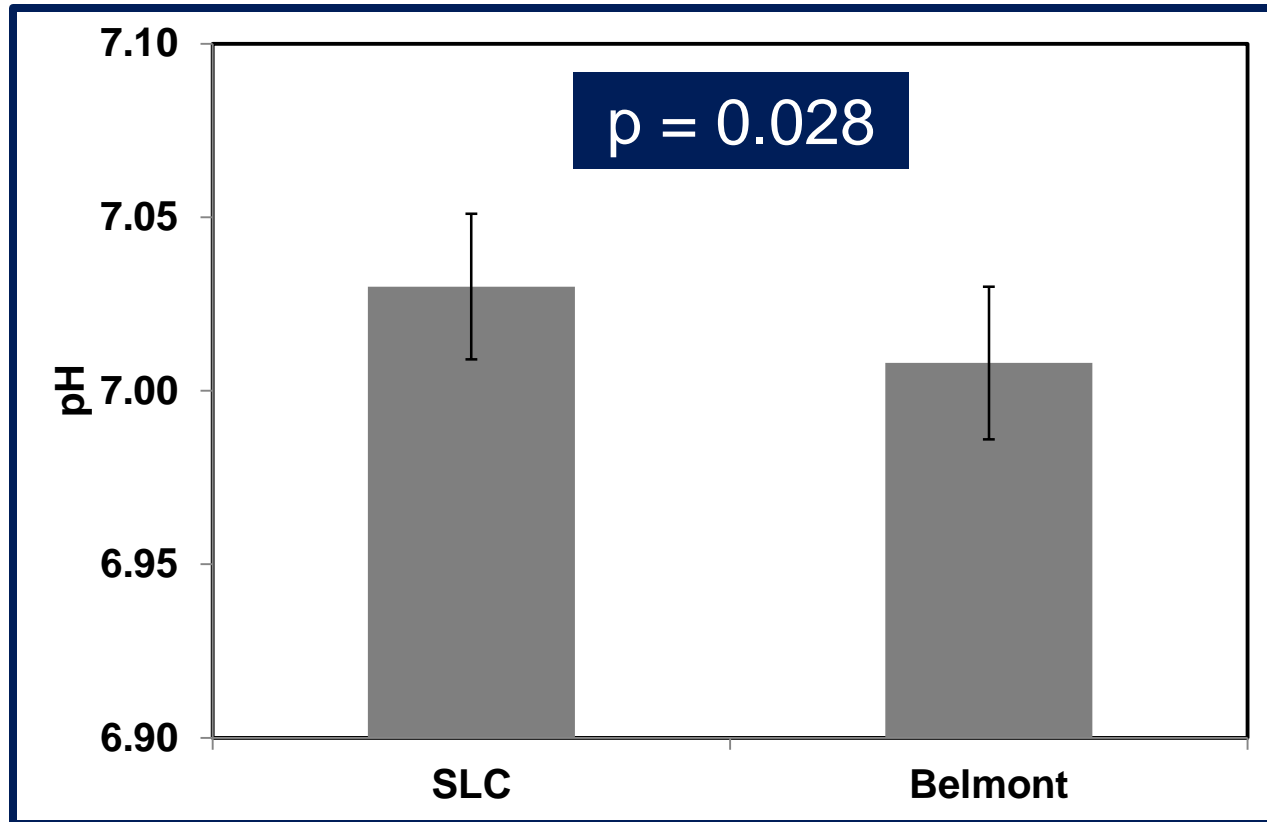
Salt Lake City VAMC

Brain Creatine Differences Between Salt Lake City (4720 ft) and Boston (20 ft)

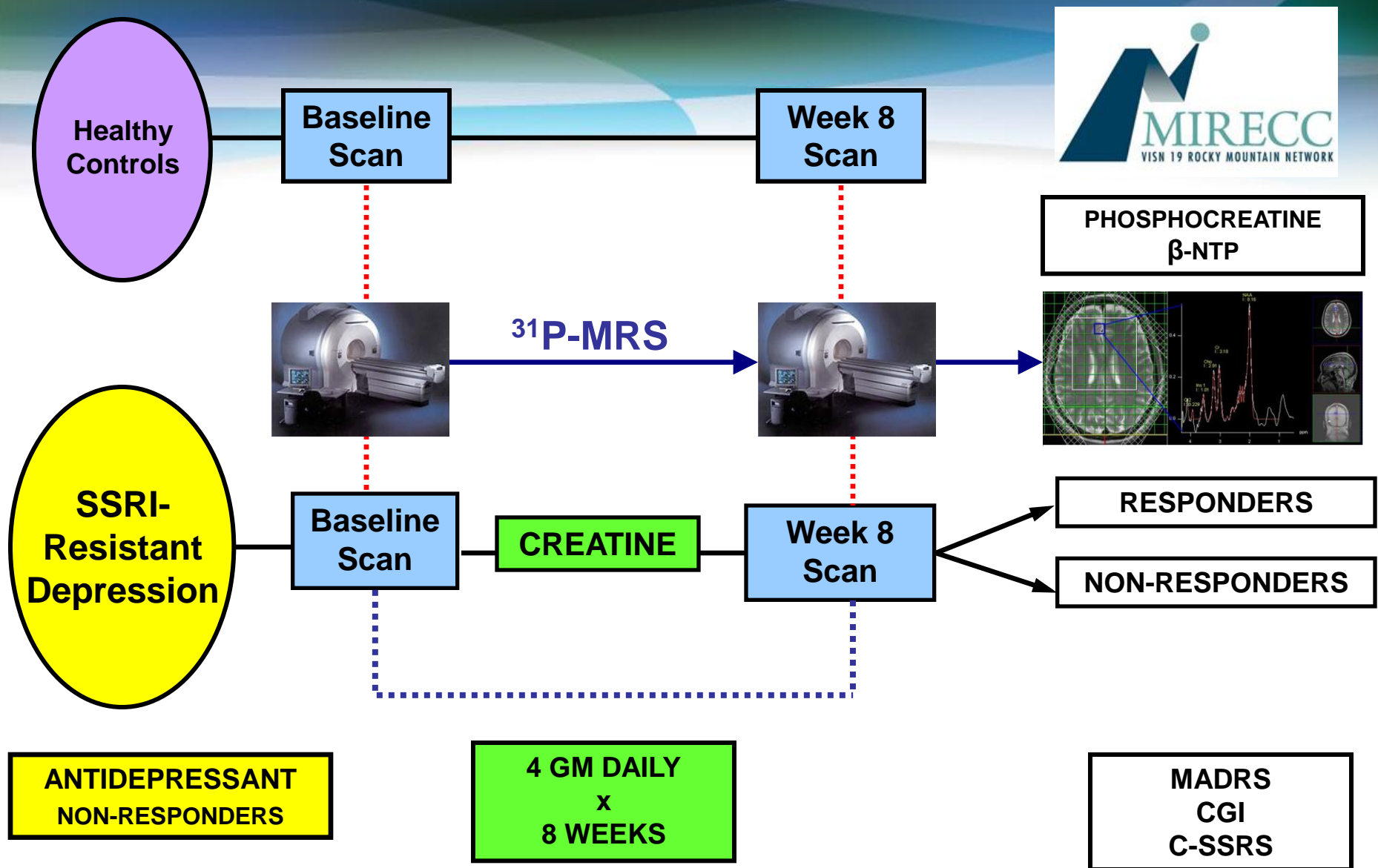


Cre = Creatine; NAA = N-Acetyl Aspartate; Glu = Glutamate;
Ins = Myo-inositol; Cho = Choline; Gln = Glutamine; Lac = Lactate

Brain pH Differences Between Salt Lake City (4720 ft) and Belmont, MA (20 ft)



	SLC (n=22) Mean (std)	Belmont (n=7) Mean (std)
pH	7.030 (0.021)	7.008 (0.022)



Creatine Clinical Trial at Salt Lake City VAMC

Thanks For Your Attention

- **MIRECC / Brain Institute Research Team**

- Deborah Yurgelun-Todd, PhD
- Perry Renshaw, MD, PhD
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- Eun-Kee Jeong, PhD
- Tracy Hellem, RN
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